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Application Number

08-509359

Filed

July 31, 1995

Paper No. 476

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US005986054A

**United States Patent** [19]**St. George-Hyslop et al.**[11] **Patent Number:** **5,986,054**[45] **Date of Patent:** **Nov. 16, 1999**[54] **GENETIC SEQUENCES AND PROTEINS  
RELATED TO ALZHEIMER'S DISEASE**[75] **Inventors:** Peter H. St. George-Hyslop; Johanna M. Rommens; Paul E. Fraser, all of Toronto, Canada[73] **Assignees:** The Hospital for Sick Children, HSC Research and Development Limited Partnership; The Governing Council of the University of Toronto, both of Canada[21] **Appl. No.:** 08/592,541[22] **Filed:** Jan. 26, 1996**Related U.S. Application Data**

[63] Continuation-in-part of application No. 08/509,359, Jul. 31, 1995, which is a continuation-in-part of application No. 08/496,841, Jun. 28, 1995, which is a continuation-in-part of application No. 08/431,048, Apr. 28, 1995.

[51] **Int. Cl.<sup>5</sup>** ..... C07K 14/00; C12P 21/06[52] **U.S. Cl.** ..... 530/350; 435/69.1[58] **Field of Search** ..... 530/350; 435/69.1[56] **References Cited****U.S. PATENT DOCUMENTS**

5,262,332	11/1993	Selkoe	436/518
5,297,562	3/1994	Potter	128/898

**FOREIGN PATENT DOCUMENTS**

2054302	4/1992	Canada
2071105	12/1992	Canada
2096911	11/1993	Canada
91/19810	12/1991	WIPO
94/00569	1/1994	WIPO
94/10569	5/1994	WIPO
94/23049	10/1994	WIPO
WO 97/03086	1/1997	WIPO
WO 97/03192	1/1997	WIPO
WO 97/03999	2/1997	WIPO

**OTHER PUBLICATIONS**Barinaga, Marcia, "New Alzheimer's Gene Found," *Science*, vol. 268:1845-1846 (1995).Barinaga, Marcia, "Missing Alzheimer's Gene Found," *Science* vol. 269:81-92 (1995).Campion, et al., "Mutations of the presenilin I gene in families with early-onset Alzheimer's disease," *Human Molecular Genetics*, vol. 4, No. 12:2373-2377 (1995).Chartier-Harlin, et al., "Early onset Alzheimer's disease caused by mutations at codon 717 of the  $\beta$ -amyloid precursor protein gene," *Nature*, vol. 353:844-846 (1991).Cruts, et al., "Molecular genetic analysis of familial early-onset Alzheimer's disease linked to chromosome 14q24.3," *Human Molecular Genetics*, vol. 4, No. 12:2363-2371 (1995).Foncin, et al., "Alzheimer's Presenile dementia transmitted in an extended kindred," *Rev. Neurol (Paris)*, vol. 141:194-202 (1985).Goate, et al., "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease," *Nature*, vol. 349:704-706 (1991).Goudsmit, et al., "Familial Alzheimer's Disease in two kindreds of the same geographic and ethnic origin: a clinical and genetic study," *J. Neurol. Sci.*, vol. 49:79-89 (1981).Gyapay, et al., "The 1993-94 Genethon human genetic linkage map," *Nature Genetics*, vol. 7:246-311 (1994).Karlinsky, et al., "Molecular and prospective phenotypic characterization of a pedigree with familial Alzheimer's disease and a missense mutation in codon 717 of the  $\beta$ -amyloid precursor protein (APP) gene," *Neurology*, vol. 42:1445-1453 (1992).Katzman, R., "Alzheimer's Disease," *N.Eng.J.Med.*, vol. 314:964-973, (1986).Levy-Lahad, et al., "A Familial Alzheimer's Disease Locus on Chromosome 1," *Science*, vol. 269:970-973 (1995).Levy-Lahad, et al., "Candidate Gene for the Chromosome 1 Familial Alzheimer's Disease Locus," *Science*, vol. 269:973-977 (1995).Mullan, et al., "A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of  $\beta$ -amyloid," *Nature Genetics*, vol. 1:345-347 (1992).Mullan, et al., "A locus for familial early-onset Alzheimer's disease on the long arm of chromosome 14, proximal to the  $\alpha$ -antichymotrypsin gene," *Nature Genetics*, vol. 2:340-342 (1992).Murrell, et al., "A mutation in the amyloid precursor protein associated with hereditary Alzheimer's Disease," *Science*, vol. 254:97-99 (1991).Nee, et al., "A family with histologically confirmed Alzheimer's Disease," *Arch. Neurol*, vol. 40:203-208 (1983).Pericak-Vance, et al., "Genetic linkage studies in Alzheimer's Disease families," *Exp. Neurol*, vol. 102:271-279 (1988).Rogaev, et al., "Analysis of the c-FOS gene on chromosome 14 and the promoter of the amyloid precursor protein gene in familial Alzheimer's disease," *Neurology*, vol. 43:2275-2279 (1993).Rogaev, et al., "Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene," *Nature*, vol. 376:775-778 (1995).Rommens, et al., "A transcription map of the region containing the Huntington disease gene," *Hum. Molec. Genet.*, vol. 2:901-907 (1993).Sherrington, et al., "Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease," *Nature*, vol. 375:754-760 (1995).

(List continued on next page.)

**Primary Examiner**—Karen Carlson**Attorney, Agent, or Firm**—Lerner, David, Littenberg, Krumholz & Mentlik[57] **ABSTRACT**

The present invention describes the identification, isolation and cloning of two human presenilin genes, PS-1 and PS-2, mutations in which lead to Familial Alzheimer's Disease. Also identified are presenilin homologue genes in mice, *C. elegans* and *D. melanogaster*. Transcripts and products of these genes are useful in detecting and diagnosing Alzheimer's disease, developing therapeutics for treatment of Alzheimer's disease, as well as the isolation and manufacture of the protein and the constructions of transgenic animals expressing the mutant genes.

**29 Claims, 12 Drawing Sheets**